23. (Amended) The method of claim [3] 1, wherein said [portion of a therapy-sensitizing gene or said portion of a cDNA] wild-type p53 gene is introduced to said tumor cell in aerosolized preparation.

REMARKS

Claims 3, 21 and 22 have been canceled without prejudice to future prosecution thereof. Claims 1-2, 6, 9, 10, 12-15, 17-20, and 23 have been amended. Applicant submits that no new matter is added with these amendments.

Claims 1, 2, 4-20, and 23 are pending in the present application (see Appendix A).

I. Amendments Made In Response To Examiner's Suggestions

Applicant has amended claim 1 following Examiner's suggestions in a telephonic interview on January 23, 1997. The amended claim 1 recites a method for enhancing a cancer therapy by delivering a wild-type 53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of the wild-type p53 gene, and subjecting the tumor cell to the cancer therapy. The Examiner stated in the interview that he will consider entering this amended claim 1 for further proceedings in the U.S. Patent and Trademark Office.

Claim 2 has been amended to make it an independent claim because the amended claim 1 is no longer a genus claim to claim 2. Claims 6, 9, 10, 12-15, 17-20, and 23 have been amended so that they will have antecedent basis in the amended claim 1.

II. The Section 112 Rejections

Applicant respectfully submits that the pending claims 1, 2, 4-20, and 23 overcome the rejection under 35 U.S.C. § 112, first paragraph, as allegedly not containing a written description of the claimed invention, and the rejection under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The written description requirement asks whether the amended claims are entitled to the benefit of the application's original filing date.

In this case, claims 1, 2, 4-20, and 23 are fully supported and disclosed in the application as originally filed with the U.S. PTO. For instance, example 1 of the application describes how to transfer a wild-type p53 gene into a tumor cell. Example 2 describes how to introduce a wild-type p53 protein into a tumor cell. Example 3 describes how to administer the drugs to cancer patients. Example 4 shows that wild-type p53 gene increases the sensitivity of glioblastoma cells to chemotherapy. Example 5 shows that wild-type p53 gene increases the sensitivity of glioblastoma cells to radiation therapy. Example 6 expands the therapy to other tumors.

The Manual of Patent Examining Procedure § 2163.03 lists four situations where an adequate written description rejection arises, none of which applies to this case.

In addition, the rejection under 35 U.S.C. § 112, second paragraph, has been rendered moot by the amendment.

Accordingly, it is respectfully requested that the rejections against claims 1, 2, 4-20, and 23 under 35 U.S.C. § 112, first and second paragraphs be withdrawn.

III. The Section 103 Rejection

Applicant respectfully submits that the pending claims 1, 2, 4-20, and 23 overcome the rejection under 35 U.S.C. § 103 as allegedly being obvious over Chen et al., Cheng et al., Eppstein et al., Itoh et al., Malkin et al. Moossa et al., Nabel et al. Srivastava, and Wu et al.

The present invention improves the therapeutic effect of a cancer therapy such as chemotherapy or radiotherapy by increasing the sensitivity of cancer cells to the therapy. The sensitivity is increased by delivering a wild-type p53 gene or wild-type p53 protein to a tumor cell which is deficient in its wild-type p53 gene. The tumor cell is then subject to the cancer therapy.

Although the prior art references describe transferring wild-type p53 gene into tumor cells, none of them describes, either alone or in combination, that wild-type p53 gene or

protein may be used to make a tumor cell deficient in its wild-type p53 gene more sensitive to cancer therapy.

Cheng et al. describe suppressing the unregulated growth of T-cell acute lymphoblastic leukemia (T-ALL) by introducing wild-type p53 gene into the T-ALL cells. However, the tumor suppression effect of wild-type p53 gene could not be equated with, and does not suggest, the therapy sensitizing effect of wild-type p53 gene.

That wild-type p53 gene is a tumor suppressor does not lead one skilled in the art to conclude that wild-type p53 gene is a therapy sensitizer. On the contrary, the growth suppressive effects of wild-type p53 gene documented in Cheng et al. would lead one skilled in the art to expect it to render cells more resistant to conventional chemotherapy and radiotherapy since chemotherapy and radiotherapy preferentially kill or suppress fast growing cells. In that regard, Cheng et al. teach away from the invention claimed in this application.

Conventional chemotherapeutic and radiation regimens employed for the treatment of cancer are known to work by killing or suppressing cells undergoing rapid growth. Chemotherapeutic drugs and radiation are known to interfere with the mitotic or cell cycle process required for cell growth and division. It is known in the prior art that nondividing cells and slow-growing cells tend to be less susceptible to chemotherapy and radiation than fast-growing cancer cells. By this rationale, the expression of wild-type p53 gene in tumor cells would be expected to reduce, rather than increase, the sensitivity of the

tumor cells to chemotherapy and radiation because wild-type p53 gene suppresses tumor cell growth.

Indeed, Vogelstein et al., Cell 70: 523-526, (1992), stated that "**p53 mutations** may therefore constitute one of the few oncogenic alterations that **increase** rather than decrease the sensitivity of cells to antitumor agents."

Therefore, Applicant's discovery that wild-type p53 gene sensitizes tumor cells to cancer therapy was unexpected from the prior art.

Unexpected or surprising results achieved by the claimed invention may be strong support for nonobviousness. Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). In this invention, the unexpected result of using wild-type p53 gene to sensitize tumor cells to chemotherapy and radiotherapy is shown in Figures 1 and 2, and Examples 4 and 5 of the specification.

Figure 1 and Example 4 show that tumor cells transduced with wild-type p53 are more sensitive to cisplatin treatment than tumor cells lacking wild-type p53. Figure 2 and Example 5 show that tumor cells transduced with wild-type p53 are more sensitive to radiation therapy than tumor cells lacking wild-type p53.

None of these results was reported in or could be inferred from the references cited by the Examiner. Therefore, Applicant submits that the unexpected result obtained with the claimed method supports nonobviousness over references cited by the Examiner.

Accordingly, the claims are now in condition for allowance and a notice to that effect is respectfully requested. If there is any fee in connection with this response, please charge Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,

LYON & LYON LLP

By _____
Anthony C. Chen
Reg. No. 38,673

ACC:kag
First Interstate World Center
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
Telephone: (619) 552-8400
Facsimile: (213) 955-0440

Appendix A: Pending Claims of Application Ser. No. 08/335,461

1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and

subjecting said tumor cell to said cancer therapy.

2. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:

delivering a wild-type p53 protein to a tumor cell which is deficient in its wild-type p53 gene, and

subjecting said tumor cell to said cancer therapy.

4. The method of claim 1 wherein said cancer therapy is radiation therapy.

5. The method of claim 1 wherein said cancer therapy is chemotherapy.

6. The method of claim 1, wherein said cancer therapy is immunotherapy.

7. The method of claim 1, wherein said cancer therapy is cryotherapy.

8. The method of claim 1, wherein said cancer therapy is hyperthermia.

9. The method of claim 1 wherein said tumor cell is selected from the group consisting of leukemia cell, lymphoma tumor cell, ovarian carcinoma cell, osteogenic sarcoma cell, lung carcinoma cell, colorectal carcinoma cell, hepatocellular carcinoma cell, glioblastoma cell, prostate cancer cell, breast cancer cell, bladder cancer cell, kidney cancer cell, pancreatic

cancer cell, gastric cancer cell, esophageal cancer cell, anal cancer cell, biliary cancer cell, and urogenital cancer cell.

10. The method of claim 1, wherein said wild-type p53 gene is in a vector.

11. The method of claim 10, wherein said vector is selected from the group consisting of adenovirus vector, retroviral vector, adeno-associated virus vector, herpes virus vector, vaccinia virus vector and papilloma virus vector.

12. The method of claim 1, wherein said wild-type p53 gene is coupled to a virus capsid or particle.

13. The method of claim 12, wherein said wild-type p53 gene is coupled to said capsid or particle through a polylysine bridge.

14. The method of claim 1, wherein said wild-type p53 gene is encapsulated in a liposome.

15. The method of claim 1, wherein said wild-type p53 gene is conjugated to a ligand.

16. The method of claim 15, wherein said ligand is an asialoglycoprotein.

17. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by direct injection.

18. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intra-arterial infusion.

19. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intracavitary infusion.

20. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intravenous infusion.

23. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell in aerosolized preparation.